EXHIBIT A

tion claim only if it proved Mitsuboshi's resale of the knives created a likelihood of confusion. As explained, this record involves no likelihood of confusion because the knives resold by Mitsuboshi were genuine. McCoy contends on appeal, however, that the jury's unfair competition verdict rests on Texas state law, which recognizes a broader range of unfair practices without proof of a likelihood of confusion. McCoy's maneuvering is to no avail.

[4] In support of its state law argument, McCoy cites *Schoellkopf v. Pledger*, 778 S.W.2d 897 (Tex. Ct. App. 1989), *error denied*, (June 13, 1990). *Schoellkopf* recognizes "unlawful business injury" as a type of unfair competition. *Id.* at 904.[2] *Schoellkopf* does not delineate the precise bounds of this broadly defined tort. It does, however, recognize that this type of unfair competition requires commission of another tort or other illegal conduct:

> Without some finding of an independent substantive tort or other illegal conduct, we hold that liability cannot be premised on the tort of "unfair competition."

Id. at 904-05. *Schoellkopf* applied this standard in a way directly relevant to the present case. A jury had awarded Pledger actual and punitive damages, finding that Schoellkopf had tortiously interfered with Pledger's contract rights and committed unfair competition. *Id.* at 899. The Texas Court of Appeals reversed the tortious interference verdict. *Id.* at 900-04. The court then reversed the unfair competition verdict, holding that Schoellkopf could not be liable for unfair competition absent tortious interference because Schoellkopf had not committed "an independent substantive tort or other illegal conduct." *Id.* at 904-05.

Likewise, Mitsuboshi has not committed an independent tort or illegal conduct justifying a finding of unfair competition under McCoy's theory on appeal. Because Mitsuboshi did not commit patent or trademark infringement, federal unfair competition, or tortious interference, no independent tort or illegality supports the verdict of unfair competition. This court also reverses that verdict.

CONCLUSION

Texas law entitled Mitsuboshi to resell the knives upon McCoy's wrongful refusal to pay for them. The trial court erred in denying Mitsuboshi judgment as a matter of law on each of the counts in McCoy's complaint — infringement of McCoy's patent or trademarks, tortious interference with McCoy's prospective business relations, and unfair competition with McCoy by reselling the knives.

COSTS

Each party shall bear its own costs.

REVERSED.

U.S. District Court
District of Delaware

The Liposome Co. v. Vestar Inc.

No. 92-332-RRM

Decided December 20, 1994

PATENTS

1. Infringement — Literal infringement (§120.05)

Infringement — Construction of claims (§120.03)

Patent infringement defendant's process for making lyophilized cake or powder that provides amphotericin B encapsulated in liposome does not literally infringe patent claims directed to process for dehydration of colloidal dispersion of liposomes, since, as used in asserted claims, process that "comprises mixing a hydrophilic compound with the colloidal dispersion of liposomes" should be construed to mean mixing hydrophilic compound with existing liposome dispersion, and since defendant does not mix hydrophilic compound with existing liposomes in process it follows in making its product.

2. Patentability/Validity — Anticipation — In general (§115.0701)

Patentability/Validity — Anticipation — Identity of elements (§115.0704)

Patent directed to process for dehydration of colloidal dispersion of liposomes is not invalid as having been anticipated by article

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[2] Other types of unfair competition recognized under Texas law include trade secret misappropriation, passing off, and misappropriation of business opportunity. *United States Sporting Prods., Inc. v. Johnny Stewart Game Calls, Inc.*, 865 S.W.2d 214, 217 (Tex. Ct. App. 1993), *error denied*, (March 30, 1994). None of these liability theories are applicable, however. McCoy has never claimed that Mitsuboshi misappropriated its trade secrets. Before trial, furthermore, McCoy voluntarily dismissed its passing off claim, and the trial court dismissed McCoy's misappropriation of business opportunity claim.

written prior to patent's issuance, since article does not disclose limitation of in vivo use that appears in patent claims, and since article therefore does not disclose each and every element in claims.

3. Patentability/Validity — Obviousness — Person of ordinary skill in art (§115.0902)

Person of ordinary skill in art, for purposes of determining whether subject matter of patent directed to process for dehydration of colloidal dispersion of liposomes would have been obvious, is liposomologist, not necessarily skilled in dehydration, who would have had graduate degree in chemistry or biochemistry, and would be experienced with liposomes, perhaps as used for delivery of drugs.

4. Patentability/Validity — Obviousness — Particular inventions (§115.0903.03)

Subject matter of patent directed to process for dehydration of colloidal dispersion of liposomes, with freeze-drying as preferred method of dehydration, would have been obvious to person of ordinary skill in art at time of invention, since liposomologist, as one of ordinary skill who approached research using lyophilization, would have been familiar with use of protectants such as sucrose in freeze-drying of objects such as cells, since liposomologist would consider problems and solutions in lyophilizing of cells as relevant to lyophilizing of liposomes due to analogy between cells and liposomes, since it was well known in field of freeze-drying at time of invention that sugar such as sucrose would preserve integrity of cells during freeze-drying, and since one skilled in art would therefore have expected that sucrose would preserve integrity of liposomes during freeze-drying.

5. Patentability/Validity — Specification — Enablement (§115.1105)

Patentability/Validity — Specification — Claim adequacy (§115.1109)

Patent directed to process for dehydration of colloidal dispersion of liposomes is not invalid as indefinite or for lack of enablement, since inventor's identification of hydrophilic compounds is sufficiently specific to put one skilled in art on notice as to what compounds inventor found suitable for process.

6. Practice and procedure in Patent and Trademark Office — Duty of candor — Citation of references (§110.0903.08)

Infringement — Defenses — Fraud or unclean hands (§120.1111)

Patent licensee's mischaracterization of article that anticipated subject of patent directed to process for dehydration of colloidal dispersion of liposomes, made during re-examination of patent, was not material misstatement of fact rendering patent invalid, since licensee disclosed existence of article to examiner and article was available to examiner to be read and evaluated, and since it has not been shown that licensee, in misstating article's significance, intended to mislead Patent and Trademark Office.

Particular patents — Chemical — Liposomes

4,229,360, Schneider, Lamy, process for the dehydration of a colloidal dispersion of liposomes, not infringed, obvious in view of prior art, and not invalid for anticipation, lack of enablement, indefiniteness, or inequitable conduct.

Action by The Liposome Co. against Vestar Inc. for patent infringement, in which defendant counterclaims for declaratory judgment of invalidity, unenforceability, and non-infringement. Following bench trial, federal district court holds that patent is not infringed, not invalid as anticipated by prior art, obvious in view of prior art, not invalid for lack of enablement or indefiniteness, and not invalid for inequitable conduct.

David A. Anderson, of Potter, Anderson & Corroon, Wilmington, Del.; S. Leslie Misrock, Rory J. Radding, Laura A. Coruzzi, Ann L. Gisolfi, and George C. Summerfield, of Pennie & Edmonds, New York, N.Y.; Allen Bloom, of Liposome Co., Inc., Princeton, N.J., for plaintiff.

Richard L. Sutton, Edmond D. Johnson, and Maryellen Noreika, of Morris, Nichols, Arsht & Tunnell, Wilmington; William E. Thomson Jr., Roland N. Smoot, and Joseph H. Chi, of Lyon & Lyon, Los Angeles, Calif.; Adam Cochran, of Vestar Inc., San Dimas, Calif., for defendant.

McKelvie, J.

This is a patent case. The Liposome Company, Inc. is the owner of United States Patent No. 4,229,360, which is directed to a process for the dehydration of a colloidal dispersion of liposomes. Liposome alleges that Vestar, Inc. is infringing the patent. Vestar has denied infringement and alleges the patent is invalid and unenforceable.

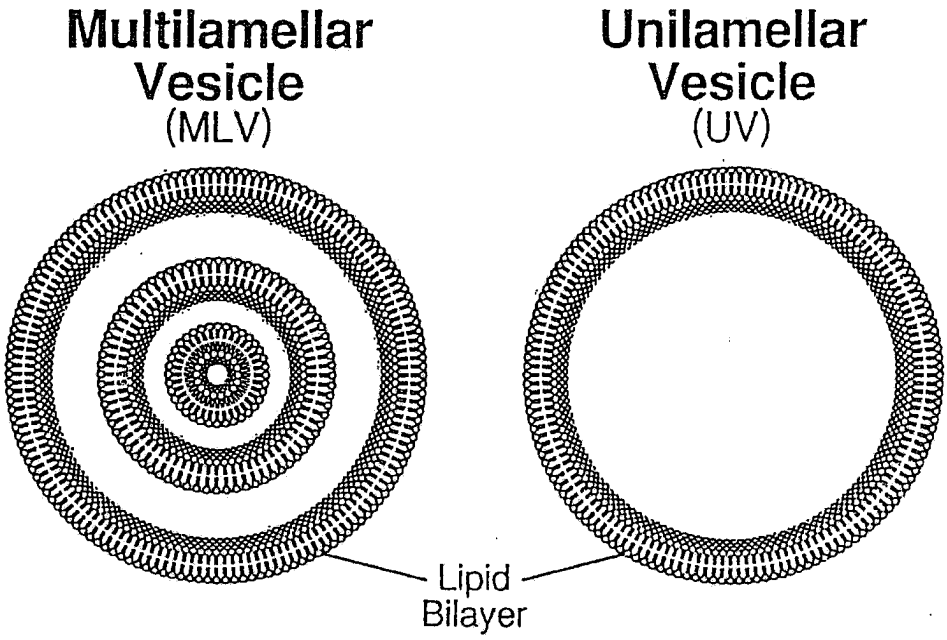
The parties tried this matter to the court from November 29 through December 7,

1993, and this is the court's post-trial decision.

FACTS

A. *The Field of the Invention and the Plaintiff's Patent*

1. *The Field of the Invention: Dehydration of Liposomes*



A liposome is a microscopic sphere or vesicle. It is like a bubble, except that where in a bubble a thin membrane surrounds air, in a liposome the membrane surrounds an aqueous solution. A liposome's membrane is a lipid bilayer, or lamella, and is approximately five nanometers thick. (There are one billion nanometers in a meter.) A lipid is an important constituent of cell structure, and is a term for a fat or fat-derived material which is characterized by being insoluble in water, but soluble in organic substances such as alcohol.

As one can make a bubble within a bubble, one can make a liposome within a liposome, so that one sphere of aqueous solution with a lipid bilayer is contained in a larger sphere of aqueous solution with a lipid bilayer. These liposomes with several bilayers are known as multilamellar vesicles ("MLVs"). Liposomes with one bilayer are unilamellar and can be large ("LUVs") or small unilamellar vesicles ("SUVs"). A small unilamellar liposome would have a diameter of from about 40 to about 100 nanometers, while a large one would have a diameter one half a micron to one micron. (There are one thousand nanometers in a micron.)

The liposome's bilayers are composed predominantly of phospholipids, a class of lipids present in plants and animals that have a hydrophilic (or water-loving) head and a hydrophobic (or water-hating) tail. When placed in water, the phospholipids organize to form a sphere (or liposome) with a bilayer in which the polar head groups align to face the water and the hydrophobic tails align to face each other. The Liposome Company has prepared and submitted the following illustrative drawing of MLV and UV liposomes.

2. *Bangham's Discovery of Liposomes*

Liposomes were discovered by Dr. Alec Bangham of Cambridge, England, in the mid 1960s. He developed a procedure for making liposomes whereby a solution of phospholipids in an organic solvent is introduced into a round bottom glass vessel. The solvent is evaporated in a vacuum, leaving a thin film of phospholipids on the bottom of the vessel. Water is added to the vessel during a hydration step, causing the phospholipids to align in bilayers. The vessel is then agitated, which causes the bilayers to close, forming multilamellar liposomes. These liposomes can be broken down to small unilamellar vesicles by sonification; that is, by applying high energy sound.

In the mid 1960s, Dr. Bangham and others studied liposomes as a model membrane system analogous to a cell membrane, as both have a bilayer phospholipid membrane. By 1970, certain scientists were investigating the use of liposomes as a container or carrier for administering enzymes or drugs into patients. As liposomes are made of natural materials, they have the advantage of being able to break down in the body and at the same time carry two kinds of drugs, one that is hydrophilic and would be in the aqueous solution in the inner compartment, and a

second that is hydrophobic and would be in the lipid bilayer.

3. *Dr. Schneider's Work*

Dr. Michel Schneider earned a doctorate in physical chemistry from Laval University in 1969. In the early 1970s, as a research scientist at Battelle Memorial Institute in Geneva, Switzerland, he began studying the use of liposomes as drug delivery vehicles. During the course of his work, he focused on liposomes' limitations, including that they were fragile and leaked and that phospholipids hydrolyze in an aqueous environment, forming lysoderivatives which destroy lipid bilayers.

Working with Bernard Lamy, Dr. Schneider sought ways to stabilize liposomal drug preparations and store them for long periods of time. He tried dehydration (removal of the water) through lyophilization (freeze-drying). Lyophilization consists of subjecting an aqueous solution to freezing followed by reduced pressure evaporation. In reduced pressure evaporation, ice undergoes a phase transformation directly into the vapor state without passing through an intermediate liquid phase. The advantage of lyophilization is that one can remove water from aqueous systems at very low temperatures where those systems would be damaged by conventional drying operations at higher temperatures. However, upon freeze-drying liposomes, Dr. Schneider found he could not reconstitute the lyophilized liposomal preparation.

Dr. Schneider theorized that having macromolecules between the liposomes would separate them from each other during dehydration and might prevent their fusing. He tried freeze-drying liposomes with a mixture of albumin, a macromolecule, and succeeded: he obtained a powder after lyophilization and when he added water the liposomes rehydrated. Dr. Schneider then successfully tested the idea with other macromolecules, including dextran, polyvinyl alcohol and gum arabic. He then tried other, lower molecular compounds, such as sucrose, and obtained good results. These agents that protect against damage by freeze-drying are known as lyoprotectants, while agents that protect against damage by freezing are known as cryoprotectants.

4. *The '360 Patent as Issued in 1980*

The Battelle Institute filed a patent application for the Schneider and Lamy invention in Switzerland on August 5, 1977. Schneider and Lamy filed the United States counterpart to the Swiss application on August 4, 1978. The application matured as United States Patent No. 4,229,360 ("the '360 patent" or the "Schneider patent") which was issued on October 21, 1980. Schneider and Lamy assigned the patent to Battelle and on October 2, 1989, Battelle assigned it to The Liposome Company, Inc. ("TLC").

The abstract submitted with the application described the invention as follows:

> The invention concerns a process for the dehydration of a colloidal dispersion of liposomes in an aqueous liquid medium, this process being aimed at extending the conservation of the liposomes and to enable their efficient use at a later date.

A colloidal dispersion is one in which the particles, in this case liposomes, are small enough that they remain suspended and do not settle out by gravity.

The specification included the following description of the process:

> Thus, an object of the present invention is a process for the dehydration of a liposome colloidal dispersion in an aqueous liquid medium, which comprises mixing a hydrophilic compound with the liposome dispersion and subjecting the obtained mixture to a dehydration operation leading to the formation of liposomes in the form of a stable powder which can be stored for a long period and from which, and with an aqueous medium, a liposome dispersion can be reconstituted.

As originally issued, the '360 patent contained five claims, with claim 1 an independent claim and the balance of the claims dependent on it. Claim 1 read:

> 1. A process for the dehydration of a colloidal dispersion of liposomes in an aqueous liquid medium, which comprises mixing a hydrophilic compound with the liposome dispersion and dehydrating the mixture to form a stable liposome containing powder which can be stored and reconstituted in an aqueous medium as a liposome dispersion.

Claims 2 through 5 read:

> 2. The process of claim 1, in which the mixture is dehydrated by first freezing said mixture of the liposome dispersion and the hydrophilic compound and, thereafter, removing water from said frozen mixture by reduced pressure evaporation to obtain said powder of liposomes.
>
> 3. The process of claims 1 or 2, wherein the liposomes consist essentially of vesicles of liquid encapsulated in a film of lipid and said mixture includes, by weight, at least as much of the hydrophilic compound as of the lipid used to form the liposomes.
>
> 4. The process of claim 3 wherein the weight ratio of the hydrophilic compound to the lipid is from 1 to 1 to 4 to 1.

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5. The process of claim 3, wherein said hydrophilic compound is selected from the group comprising dextran, gum arabic, polyvinyl alcohol, polyvinyl pyrrolidone and oxalbumin.

B. *Vestar Reviews the Schneider Patent*

Vestar began its research and development on a liposomal amphotericin B product during 1985. Amphotericin B is a broad spectrum antifungal drug.

At the time it began that work, Vestar was aware of the Schneider '360 patent. In 1986, it obtained an opinion from the law firm of Lyon & Lyon on the validity of the patent. In a letter dated July 21, 1986, the firm offered its opinion that in view of publications not considered by the Patent Office, if litigated, the claims of the '360 patent would be regarded as invalid on the basis of 35 U.S.C. § 103, as it would have been obvious to one of ordinary skill in the art to utilize a hydrophilic compound in a liposome dispersion to stabilize the dispersion during freeze-drying. The publications identified by counsel in the opinion are three articles by Alan MacKenzie, published or presented in 1966, 1975 and 1976.

The firm also reported that two scientists, Drs. John and Lois Crowe, had attempted to but had been unable to duplicate the examples in the patent. The firm offered its opinion that if the examples of the patent cannot be repeated and successful results obtained, the specification may not be regarded as enabling and, in that instance, the claims of the '360 patent would be invalid for failing to fulfill the statutory requirements of 35 U.S.C. § 112.

C. *Vestar's AmBisome*

Vestar's AmBisome is a lyophilized cake or powder that provides amphotericin B encapsulated in a liposome. It is used to treat life-threatening systemic fungal infections that typically occur in patients with an immune system compromised by diseases, such as cancer or AIDS, or treatment given to recipients of organ and bone marrow transplants.

In distributing its product, Vestar notes that AmBisome contains sucrose to preserve the structural integrity of the liposomes and that the powder is rehydrated with sterile water for injection. When rehydrated, the liposomes in AmBisome are small unilamellar vesicles.

Vestar preforms six basic steps in making AmBisome. They are an organic step, hydration, homogenization, filtration, filling and lyophilization.

The organic step involves formation of the drug-lipid complex and the subsequent drying of the complex. Since amphotericin B is not soluble in aqueous solution, it is first necessary to put the amphotericin B in a condition where it can be subsequently incorporated into liposomes. To do so, selected lipids and amphotericin B are complexed in an acidified organic solution and dried to form a powder which is soluble in an aqueous solution.

During hydration, a spray-dried powder containing lipids and amphotericin B is introduced into a mixing tank that contains an aqueous solution of sucrose and a buffering agent, disodium succinate. Liposomes are formed at this stage, both multilamellar large vesicles and unilamellar small vesicles. As the liposomes are formed in the presence of sucrose in solution, sucrose is found both on the inside and the outside of the liposomes.

At the third stage, homogenization, the MLVs are converted to SUVs by pumping the mixture through a homogenizer, which injects it through a narrow orifice at a very high pressure to a receiving tank, which is also a mixing tank. To obtain the correct size and distribution of liposomes, the mixture is passed through the homogenizer six times.

The mixture is then filtered three times, first through a .45 micron filter, then through a .2 micron filter. The final filtration is through a .22 micron filter, where the liquid AmBisome is then pumped into vials.

At the final stage in the preparation the liquid AmBisome is lyophilized to the cake or powder Vestar calls AmBisome. It can be stored for over a year and is reconstituted with sterile water to recover the colloidal dispersion of amphotericin B containing liposomes which are administered *in vivo*. The weight ratio of hydrophilic compound to lipid is about 3 to 1.

Vestar contends this process does not infringe the claims of the '360 patent. It contends Schneider claims a process that comprises mixing the hydrophilic compound with a liposome dispersion, whereas Vestar mixes the compound with the lipid and amphotericin B as the liposomes are being formed. Schneider's process adds the sucrose to the outside of the liposomes. Vestar's process mixes the sucrose with the lipids such that sucrose is on the inside and the outside of the liposomes.

By 1987, Vestar had optimized its formulation and lyophilization process and began to follow through on the pre-investigational new drug development of the product. In March of 1987, it entered into a joint venture with Lyphomed, Inc. to develop an array of

liposome-encapsulated products including a liposomal amphotericin B product.

Vestar began selling AmBisome in 1989.

D. *Battelle Assigns the '360 Patent to The Liposome Company*

In January of 1988, personnel from Vestar and its counsel met with Dr. Schneider in Geneva and proposed that Battelle grant to Vestar a non-exclusive license under the '360 patent, including the right to use the patented method in manufacturing amphotericin B. However, in July of 1988, Battelle informed Vestar that it had entered into an agreement transferring rights under the patent to another party.

That other party was TLC. TLC had invested considerable time and effort over a number of years in working to develop an efficient technique to lyophilize liposomes. As TLC's Chief Science Officer, Dr. Marc J. Ostro, reported to a prospective client in a November, 1988 letter, the company had identified the Schneider patent and had entered into a licensing agreement with Battelle after TLC had been unable to circumvent it. Dr. Ostro added the following description of those efforts:

> You will notice in Claim #1 of the Battelle patent that the authors added the hydrophilic compound to the outside of the liposomes and do not include it in the formation process. Therefore, no sugar will be on the inside of the liposomes. This process resulted in the data shown in Table 1 of the patent. Obviously, 60-70% protection of liposomes is not adequate for a pharmaceutical product. We have found, however, that if the sugar is inside and outside, you can get in excess of 90% protection.
>
> The logical next question is "if you put the sugar *inside* as well as outside, why doesn't that get around the patent"? If you use passive entrapment techniques whereby you only encapsulate 50% of the drug, then the free drug must be removed from the liposomes subsequent to production. When you do this, you also remove the external sugar and this sugar must be replaced thereby violating the patent. The only way around this, we thought, was to remove the entrapped doxorubicin by column chromatography using a column pre-equilibrated with the same concentration of the sugar as you used during the formation process. One could then logically assume that, while you are removing the drug you are not removing the sugar and therefore the sugar would not have to be replaced. Fortunately for us, this is not exactly the case. While the total sugar concentration may not change, the individual sugar molecules will. Fifty percent of the sugar in the final liposome suspension will have been added externally on the gel filtration column. This, once again, violates the patent. It was therefore our internal opinion as well as the external legal opinion that if a water soluble additive was used, it would violate this patent.

E. *The Liposome Company's Janoff Patent*

During the course of the trial, the parties offered evidence on a second patent owned by TLC, U.S. Patent No. 4,880,635 (the "'635 patent" or the "Janoff patent"), which was issued on November 14, 1989. This patent also relates to the dehydration of liposomes using the hydrophilic compound sucrose. Vestar contends that in connection with the prosecution of the European counterpart to this patent, TLC made certain statements about the Schneider patent that are relevant to the claims in issue in this action.

Andrew S. Janoff, Pieter R. Cullis are two of the inventors of the subject of the '635 patent. The patent is based on an application filed on August 8, 1984. It includes an independent claim and eight dependent claims. The independent claim, Claim 1, reads:

> 1. A dehydrated liposome preparation comprising liposomes having a bilayer membrane and one or more protective sugars, wherein the protective sugars are present at both the inside and outside surfaces of the liposome membrane so that the liposomes have retained a substantial portion of their internal contents during dehydration and retain a substantial portion of their contents upon subsequent rehydration.

F. *The Liposome Company Applies for a Reexamination of the Schneider Patent*

In March of 1990, TLC asserted the Schneider patent against Vestar. Vestar responded that it did not infringe the claims of the Schneider patent and that its allegedly infringing product, AmBisome, is produced under U.S. Patent 4,857,319 (the "Crowe Patent"), which issued to the University of California and is licensed to Vestar.

On January 11, 1991, TLC filed a request for reexamination of the '360 patent with the United States Patent and Trademark Office ("PTO") pursuant to 37 C.F.R. § 1.510 in light of two articles not cited during the prosecution of the original application but that were cited during the prosecution of the Crowe patent. The first article, by Efraim Racker, was published in 1972 in the *Journal of Membrane Biology*, and is entitled "Reconstitution of Cytochrome Oxidase Vesicles and Conferral of Sensitivity to En-

ergy Transfer Inhibitors." The second article, by F. Sreter, N. Ikemoto and J. Gergely, was published in 1970 in *Biochemica et Biophysica Acta*, and is entitled "The Effect of Lyophilization and Dithiothreitol on Vesicles of Skeletal and Cardiac Muscle Sarcoplasmic Reticulum." In its request, TLC stated that these two articles speak to lyophilization of liposomes and could be read as suggesting that using sucrose during lyophilization would prevent permeability, or enhance the integrity of the lipid bilayer.

In his article, Racker describes a study of respiratory control and cytochrome *c* oxidase activity in vesicles formed from phospholipids and the mitochondrial transmembrane enzyme, cytochrome *c* oxidase. He discloses that using sucrose during lyophilization of cytochrome *c* oxidase vesicles prevents loss of respiratory control. That is, using sucrose during lyophilization maintains the membrane's integrity and prevents protons from reentering the vesicle. In seeking to distinguish Racker from the claims in '360 patent, TLC argued during reexamination that maintenance of respiratory control in the cytochrome *c* oxidase system indicates nothing with regard to the physical integrity of the vesicle to drugs such as those encapsulated by the liposome vesicles of the patent.

Sreter describes a study of the Ca++ uptake and ATPase enzyme activity of vesicles composed of fragments of muscle sarcoplasmic reticulum membranes and reports that after lyophilization, no loss of Ca++ uptake or ATPase enzyme activity was observed even after 4 months of storage. TLC argued that while Sreter discloses that the muscle was homogenized in the presence of sucrose, nothing in the article suggests the sucrose was considered protective or important to the lyophilization process.

In March of 1991, the PTO granted TLC's request for reexamination and in a June, 1991 office action rejected all five claims of the '360 patent as being unpatentable under 35 U.S.C. §§ 102(b) and 103, as anticipated or rendered obvious by Racker and Sreter. The examiner found both references disclose a process for dehydrating a colloidal dispersion of liposomes in an aqueous liquid medium. In particular, the examiner found that Racker discloses the mixing of a hydrophilic compound with the liposome containing powder which can be stored and reconstituted in an aqueous medium as a liposome dispersion, and that Sreter discloses the mixing of a hydrophilic compound with the liposome dispersion and dehydrating the mixture to form a stable liposome containing powder which can be stored and reconstituted in an aqueous medium as a liposome dispersion.

In rejecting TLC's arguments on the patentability of the claims, the examiner noted that the dehydrating process described in the claims did not appear to be materially different from the dehydrating processes of Racker and Sreter and that the claims as written did not mention the inclusion of drugs or the "physical integrity of the vesicle to drugs" that are encapsulated.

In response to the rejection, TLC proposed the following amendments to the five claims, with the new matter underlined [italics] and the deleted words bracketed:

1. A process for the dehydration of a colloidal dispersion of liposomes [in an aqueous liquid medium] which comprises mixing a hydrophilic compound with the *colloidal dispersion of the liposomes in an aqueous liquid medium*, [liposome dispersion] and dehydrating the mixture to form a stable [liposome containing] powder which can be stored and reconstituted in an aqueous medium *to recover the colloidal dispersion of liposomes which is suitable for administration in vivo* [as a liposome dispersion].

2. The process of claim 1, in which the mixture is dehydrated by first freezing said mixture of the liposome dispersion and the hydrophilic compound and, thereafter, removing water from said frozen mixture by reduced pressure evaporation to obtain said powder [of liposomes].

3. The process of claims 1 or 2, wherein the liposomes consist essentially of vesicles of liquid encapsulated in a [film of a] lipid *bilayer* and said mixture includes, by weight, at least as much of the hydrophilic compound as of the lipid used to form the liposomes.

4. The process of claim 3 wherein the weight ratio of the hydrophilic compound to the lipid is from 1 to 1 to 4 to 1.

5. The process of claim 3, wherein said hydrophilic compound is selected from the group comprising dextran, gum arabic, polyvinyl alcohol, polyvinyl pyrrolidone and oxalbumin.

And it proposed to add the following claims:

6. A process for the dehydration of a colloidal dispersion of liposomes, which comprises mixing a hydrophilic compound with the colloidal dispersion of the liposomes in an aqueous liquid medium, and dehydrating the mixture to form a stable powder which can be stored and reconstituted in an aqueous medium to recover the colloidal dispersion of liposomes which is suitable for oral administration.

7. The process of claim 6, in which the mixture is dehydrated by first freezing said mixture of the liposome dispersion and the hydrophilic compound and, thereafter, removing water from said frozen mixture by reduced pressure evaporation to obtain said powder.

8. The process of claims 6 and 7, wherein the liposomes consist essentially of vesicles of a liquid encapsulated in a lipid bilayer and said mixture includes, by weight, at least as much of the hydrophilic compound as of the lipid used to form the liposomes.

9. The process of claim 8 wherein the weight ratio of the hydrophilic compound to the lipid is from 1 to 1 to 4 to 1.

10. The process of claim 8, wherein said hydrophilic compound is selected from the group comprising dextran, gum arabic, polyvinyl alcohol, polyvinyl pyrrolidone and ox- albumin.

11. A process for the dehydration of a colloidal dispersion of liposomes, which comprises mixing a hydrophilic compound with the colloidal dispersion of the liposomes in an aqueous liquid medium and dehydrating the mixture to form a stable powder which can be stored and reconstituted in an aqueous medium to recover the colloidal dispersion of liposomes which is suitable for injection into a patient.

12. The process of claim 11, in which the mixture is dehydrated by first freezing said mixture of the liposome dispersion and the hydrophilic compound and, thereafter, removing water from said frozen mixture by reduced pressure evaporation to obtain said powder.

13. The process of claims 11 or 12, wherein the liposomes consist essentially of vesicles of a liquid encapsulated in a lipid bilayer and said mixture includes, by weight, at least as much of the hydrophilic compound as of the lipid used to form the liposomes.

14. The process of claim 13 wherein the weight ratio of the hydrophilic compound to the lipid is from 1 to 1 to 4 to 1.

15. The process of claim 13, wherein said hydrophilic compound is selected from the group comprising dextran, gum arabic, polyvinyl alcohol, polyvinyl pyrrolidone and oxalbumin.

In support of these proposed amendments, TLC noted:

> The present invention provides a method for dehydrating liposomes useful as delivery vehicles *in vivo*. Using the dehydration method of the invention, a storable powder is obtained from a colloidal dispersion of liposomes which then can be reconstituted in an aqueous medium to recover the colloidal dispersion of liposomes which remain usable for a variety of *in vivo* applications. Liposomes prepared according to the invention can be administered to patients, *e.g.*, by injection or orally, to deliver a specific quantity of bioactive agent such as a drug or imaging agent. No known reference describes or suggests the method of the present invention.

TLC reviewed Racker and Sreter in its statement to the PTO in support of its amended claims. As to Racker, it reported:

> Racker's sole observation was the maintenance of respiratory control in the cytochrome oxidase vesicles lyophilized in the presence of sucrose. As explained above, respiratory control is solely a measure of enzyme activity, and has nothing to do with the stability of liposomes.

And as to both articles, it reported:

> Neither Racker nor Sreter disclose the lyophilization of liposome delivery systems, *i.e.* liposomes which can be used *in vivo* as delivery vehicles for therapeutic or diagnostic applications. Each reference relates only to an *in vitro* study of the activity of certain transmembraneous enzymes using uncharacterized lipid vesicles that may include liposomes, or a mixture of liposomes and micelles, and does not relate to the processing of liposomes used as a delivery vehicle at all.

G. *Patent Office Issues Reexamination Certificate With Amended Claims*

In September, 1991, the PTO issued a Notice of Intent to Issue Reexamination Certificate, confirming claims 1 through 3 as amended and claims 4 and 5 as originally granted, and adding the new claims 6 through 15, noting:

> The instant claims are concerned with a method for dehydrating a colloidal dispersion of liposomes suitable for administration *in vivo*, by mixing a hydrophilic compound with the liposome dispersion then dehydrating to form a stable powder which upon reconstitution in an aqueous medium forms the dispersion of liposomes suitable for *in vivo* administration to a patient.
>
> The prior art of Racker and Sreter appear to disclose enzyme function *in vitro* not *in vivo*. Also see applicants [sic] arguments pages 11-16, 16-18 and 19-22.

On November 5, 1991, the PTO issued Reexamination Certificate B 14,229,360 to The Liposome Company.

In November, 1991, Vestar obtained a supplemental opinion from counsel at Lyon & Lyon. In that opinion, counsel advised Vestar that the '360 patent would be found

invalid as anticipated under 35 U.S.C. § 102 or obvious under 35 U.S.C. § 103 in light of the Racker article.

H. *The Liposome Company's Prosecution of the European Counterpart of the Janoff Patent*

On August 7, 1985, TLC filed an application with the European Patent Office for a counterpart of the '635 patent. During the prosecution of that application, the examiner rejected certain claims in light of the Schneider patent. In response to the rejection, TLC's counsel wrote to the examiner on October 8, 1990:

> 3) Regarding the art rejection of claims 1, 2, 7-8 (new claims 4-5) DI (GB 2,002,319, Schneider et al.) teaches the dehydration of liposomes by mixing a liposome dispersion with a sugar and then drying the preparation.
>
> In contrast, Applicant's claim 1 is directed to the preparation of liposomes in the presence of a protective sugar, then dehydrating the preparation. In Applicant's preparation, the liposomes contain the protective sugar on BOTH SIDES of the lipid bilayers ("*preparing* a liposome which includes . . . sugars . . ."); as contrasted with the Schneider patent which contains sugar on only the exterior of the liposomes. In D1, the sugar is not included in the liposomes. Applicant has performed a comparative test of the two methods (results shown in Table 2) and demonstrated that surprisingly, more of the entrapped material is left after dehydration with sugar on both sides of the membrane (Applicant's method) than when dehydration is performed with sugar on only the outside of the membranes (Schneider method).

On receiving this letter, the examiner responded that the claim would still be rejected for lack of novelty based on Schneider and noted that the presence of protective sugars on both sides of the liposomal membrane is not mentioned in the claim. In reply to that response, TLC amended its claim to include "wherein said sugars are present at both the inside and outside surfaces of the liposome membranes." The European Patent Office eventually granted the European patent in November of 1992.

I. *Pre-Trial and Trial Proceedings*

TLC filed this action against Vestar in June of 1992. In the complaint filed pursuant to 35 U.S.C. § 271, TLC alleges Vestar is infringing claims of the '360 patent by making dehydrated colloidal dispersions of liposomes and that Vestar's infringement has been willful and deliberate. The complaint is at Docket Item ("D.I.") 1. Vestar answered the complaint by denying infringement, and asserted seven affirmative defenses, including that the claims of the patent should be found invalid as obvious and that the patent should be declared unenforceable because of alleged misrepresentations TLC made to the PTO during the reexamination. Vestar also counterclaimed for a declaratory judgment of invalidity, unenforceability and noninfringement for the reasons set forth in its affirmative defenses.

On August 13, 1992, the court entered a scheduling order that provided for completion of discovery by August 2, 1993, with each party designating its expert witnesses on or before June 1, 1993, and each designating rebuttal expert witnesses on or before July 1st. The order confirmed that the final pretrial conference would be on August 12, 1993, and a non-jury trial would begin on November 11, 1993. D.I. 11.

In February of 1993, Vestar moved to amend its answer and counterclaim to assert a claim for a declaratory judgment that the claims of the Janoff patent are invalid. By an Opinion and Order dated May 13, 1994, court denied Vestar's motion to amend. D.I. 44 and 45. Thereafter, the court rescheduled the pretrial conference to November 12, 1993, and the trial to begin on November 29, 1993.

On May 17, 1993, Vestar filed a complaint seeking a declaration that the claims of TLC's Janoff patent are invalid and not infringed by Vestar, and that the Janoff patent is unenforceable. *Vestar, Inc. v. The Liposome Company*, C.A. No. 93-232-RRM. The court stayed that case pending the outcome of a reexamination of the Janoff patent.

At the November 12, 1993, pretrial conference in this case, the court granted TLC's motion to preclude Vestar from calling Thomas D. Kiley to testify as an expert in the area of patent licensing practices and royalty rates, finding Vestar had failed to identify Kiley as a witness within the time provided by the court's scheduling order. The court granted Vestar's motion to preclude TLC from seeking relief based on a claim of infringement under the doctrine of equivalents, finding TLC had failed to disclose, in response to Vestar's discovery requests, that it intended to rely on the doctrine of equivalents and consequently had failed to identify in discovery the facts and testimony it would offer in support of a claim based on that doctrine. D.I. 129 and D.I. 139.

DISCUSSION

I. *Basis for Jurisdiction*

The court has jurisdiction to hear and resolve the plaintiff's claim of patent infringement pursuant to 28 U.S.C. § 1338(a), and the defendant's counterclaims pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 *et seq.* and under 15 U.S.C. § 1121, the doctrine of pendent jurisdiction and Federal Rule of Civil Procedure 13.

As both the plaintiff and defendant are incorporated in Delaware, plaintiff properly brought the action in this district under 28 U.S.C. § 1400.

II. *Is Vestar Infringing the '360 Patent by Manufacturing and Selling AmBisome?*

TLC contends Vestar is infringing claims 1, 2, 3, 4, 11, 12, 13 and 14 of the '360 patent, by manufacturing and selling AmBisome. It offers the following element by element comparison of the claims and the AmBisome process:

CLAIM 1 A process for the dehydration of a colloidal dispersion of liposomes which comprises: mixing a hydrophilic compound with the colloidal dispersion of liposomes in an aqueous medium and dehydrating the mixture to form a stable powder which can be stored and reconstituted in an aqueous medium to recover the colloidal dispersion of liposomes which is suitable for administration *in vivo*.	VESTAR'S PROCESS AmBisome is a freeze dried drug containing liposome product. Vestar's AmBisome process includes making and dehydrating, by lyophilization, a colloidal dispersion of liposomes. Mixing an aqueous sucrose (hydrophilic compound) solution with a colloidal dispersion of liposomes using mixing tanks, mixers, an homogenizer and a pump to obtain a mixture. Dehydrating the mixture in a lyophilizer to form a stable powder which can be stored for over a year. AmBisome is reconstituted by rehydration with sterile water to recover the colloidal dispersion of amphotericin B containing liposomes which are administered *in vivo*.
CLAIM 2 The process of claim 1, in which the mixture is dehydrated by first freezing said mixture of the liposome dispersion and the hydrophilic compound and, thereafter, removing water from said frozen mixture by reduced pressure evaporation to obtain said powder of liposomes.	VESTAR'S PROCESS AmBisome is dehydrated by lyophilization.
CLAIM 3 The process of claim 1 . . . wherein . . . said mixture includes, by weight, at least as much of the hydrophilic compound as of the lipid used to form the liposomes.	VESTAR'S PROCESS AmBisome contains 900 mg sucrose and 349 mg lipid which is a weight ratio of the hydrophilic compound to lipid of over 2.5 to 1. Dr. Eley testified that the ratio is about 3:1.
CLAIM 4 The process of claim 3 wherein the weight ratio of the hydrophilic compound to the lipid is from 1-to-1 to 4-to-1.	VESTAR'S PROCESS AmBisome contains 900 mg sucrose and 349 mg lipid which is a weight ratio of the hydrophilic compound to lipid of over 2.5 to 1. Dr. Eley testified that the ratio is about 3:1. (Eley, Trial Tr. at 1162: 17-25).

In addition, TLC notes that claims 11-14 parallel claims 1-4, but call for administration by injection and that AmBisome infringes these claims as it is administered by intravenous injection.

The court follows a two step process in resolving TLC's contention that Vestar's process infringes the patent's claims. First, the court must determine the scope of the claims at issue. *Autogiro Co. of Am. v. United States*, 384 F.2d 391, 401 [155 USPQ 697] (Ct. Cl. 1967). Though construction of the claims and their scope is a question of law, *Senmed, Inc. v. Richard-Allan Medical Indus., Inc.*, 888 F.2d 815, 818 [12 USPQ2d 1508] (Fed. Cir. 1989), the meaning of claim language may turn on underlying issues of fact, *Perini Am., Inc. v. Paper Converting Mach. Co.*, 832 F.2d 581, 584 [4 USPQ2d 1621] (Fed. Cir. 1987), which arise where there is a genuine evidentiary conflict over the term's meaning, *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1579 [12 USPQ2d 1382] (Fed. Cir. 1989). Claim language should normally be interpreted as it would be by one reasonably skilled in the art. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 867 [228 USPQ 90] (Fed. Cir. 1985). Typically, this will require the court to read the words of a claim as if the inventor intended them to express their ordinary meaning. An inventor may, however, invest certain claim language with a unique definition. In either case, the court may look to extrinsic evidence to determine the meaning of the words an inventor has used in a claim. This extrinsic evidence may take the form of discussion found in the patent's specification and prosecution history, and expert testimony regarding the meaning of certain words in a claim as they would be understood by those skilled in the art. *See McGill Inc. v. John Zink Co.*, 736 F.2d 666 [221 USPQ 944] (Fed. Cir.) (referring to the file history, specification, and expert testimony as extrinsic evidence to construe words in the claims of the patent), *cert. denied*, 469 U.S. 1037 (1984); *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565 [219 USPQ 1137] (Fed. Cir. 1983) (employing the specification and prosecution history as extrinsic evidence to interpret the claims of the patent).

Second, once the court determines the scope and meaning of the claims, it must determine whether the accused product infringes them. *Palumbo v. Don-Joy Co.*, 762 F.2d 969, 974 [226 USPQ 5] (Fed. Cir. 1985). That is, the court must determine whether the properly interpreted claims read on the accused product.

A. *"Mixing a Hydrophilic Compound with the Colloidal Dispersion of the Liposomes"*

Vestar rests its infringement defense on the language in claim 1 that describes a process which "comprises mixing a hydrophilic compound with the colloidal dispersion of the liposomes." Vestar contends it does not infringe that or the other claims of the patent because it does not mix the sugar solution with liposomes in the process it follows to make AmBisome. Rather, Vestar mixes the sucrose with the lipids and amphotericin B at the time it forms the liposomes.

B. *Does "Mixing" Mean to Obtain a Mixture?*

TLC contends the term "mixing" as used in the claims of the '360 patent means obtaining a mixture of a hydrophilic compound and a liposome dispersion prior to dehydration and any activity or operation which results in forming or maintaining the mixture prior to the dehydration. It contends it does not matter how the mixture is obtained, what type of liposomes are used, whether the liposomes are added to a hydrophilic compound, or vice versa, or are made in a hydrophilic compound, as long as there is a mixture prior to dehydration so that the liposomes are preserved and can be recovered upon rehydration.

At trial, TLC called Peter Cullis to testify on how one skilled in the art would understand the claimed invention and the claim terms. Dr. Cullis earned a doctorate in physics from the University of British Columbia in 1972. In 1973, he began to study the biophysics of membrane systems employing liposomes. At about that time he also initiated work on the reconstitution of membrane proteins. He is a former president of a Liposome Company subsidiary and is now a Professor of Chemistry at the University of British Columbia. Dr. Cullis testified that Schneider's invention was to mix a hydrophilic compound with a liposome dispersion prior to lyophilization, that it does not matter how one arrives at that mixture, and it does not exclude having the compound on the inside as well as the outside of the liposomes. Thus, he stated: "This is a basic discovery . . . if you have a mixture . . . of a hydrophilic compound such as sucrose mixed with liposomes, you can then dehydrate it and then recover those liposomes subsequently."

In support of its reading of the language of the claim, TLC notes that the claim includes the transitional phrase "comprising," which it suggests should be read as identifying an open-ended description of a two step process of (1) mixing a hydrophilic compound with a colloidal dispersion of liposomes and (2) dehydrating the mixture to obtain a stable powder which can be reconstituted to recover the liposome dispersion which is suitable for use *in vivo*. TLC contends that although Vestar's process may include more than two steps, it includes these two steps and therefore it infringes.